Biology from an EE perspective
Lecture 9

Chemical signaling at the cell surface

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Lecture Overview

- Chemical signaling very widely used in organisms
  - A large window to sensing the environment via chemicals
  - Widely used for communication between cells
  - Electrical signaling often terminated with chemical signaling
- Chemical signaling can be both proximal & remote
- Signaling paradigms
- Examples

Figure credits: Unless mentioned, all jpeg images are from the site of *Molecular Cell Biology* by Lodish et al., published by W H Freeman & Co

Chemical signaling

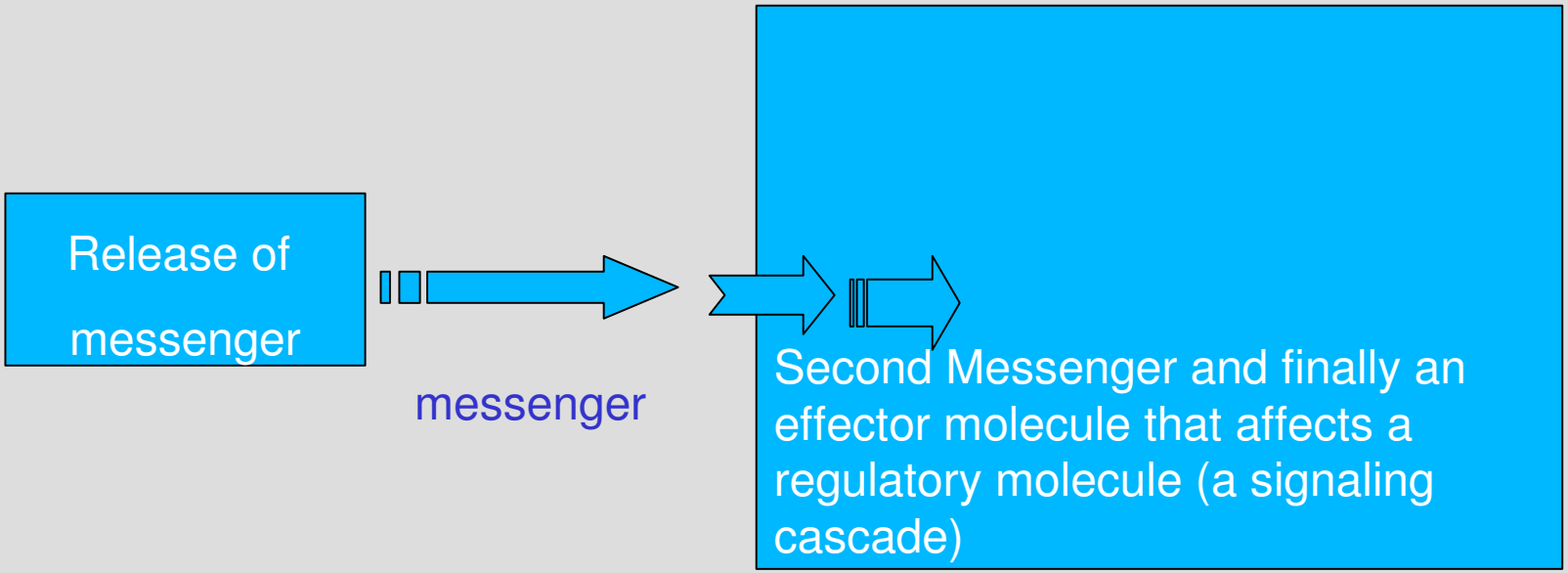
- Used for homeostatis, for responding to environmental stimuli and for cell cycle control
- Some examples are:
  - Control of blood pressure by modulating blood vessel cross-section
  - Regulation of metabolic rates
  - Sensing and control of signaling for organ growth via cell division
  - Muscle contraction
  - Response to temperature shock

Chemical signaling some possibilities

- Signaling can be short range
  - Autocrine: Signaling with target sites on the same cell (such as, cytokine interleukin1 in monocytes. growth factors released by certain tumor cells)
  - Paracrine: Signaling with target sites on cells in proximity neurotransmitters (such as, across a synapse)
- Signaling can be long range
  - Endocrine: Signaling with target sites on cells at a distance, such as in hormonal control in which the signaling molecules are normally carried by the blood

How can one transfer a signal across a cell membrane?
Molecules should not be transported across!

Signaling process



Ligand → Receptor → Signal transduction

Signaling process

- Signaling happens via a series of processes – is really a signaling cascade
  - Release of signaling molecule
  - Diffusion of the signaling molecule to a receptor and attachment to a receptor
  - Release of a second messenger within a cell
  - Trigger of some chemical process by the second messenger, such as activation or deactivation of an enzyme molecule or triggering an ion channel protein
  - Degradation or removal of the second messenger
  - Deactivation of the signal transduction protein
  - Desensitization of the receptor at high conc of signaling mol

Possibilities

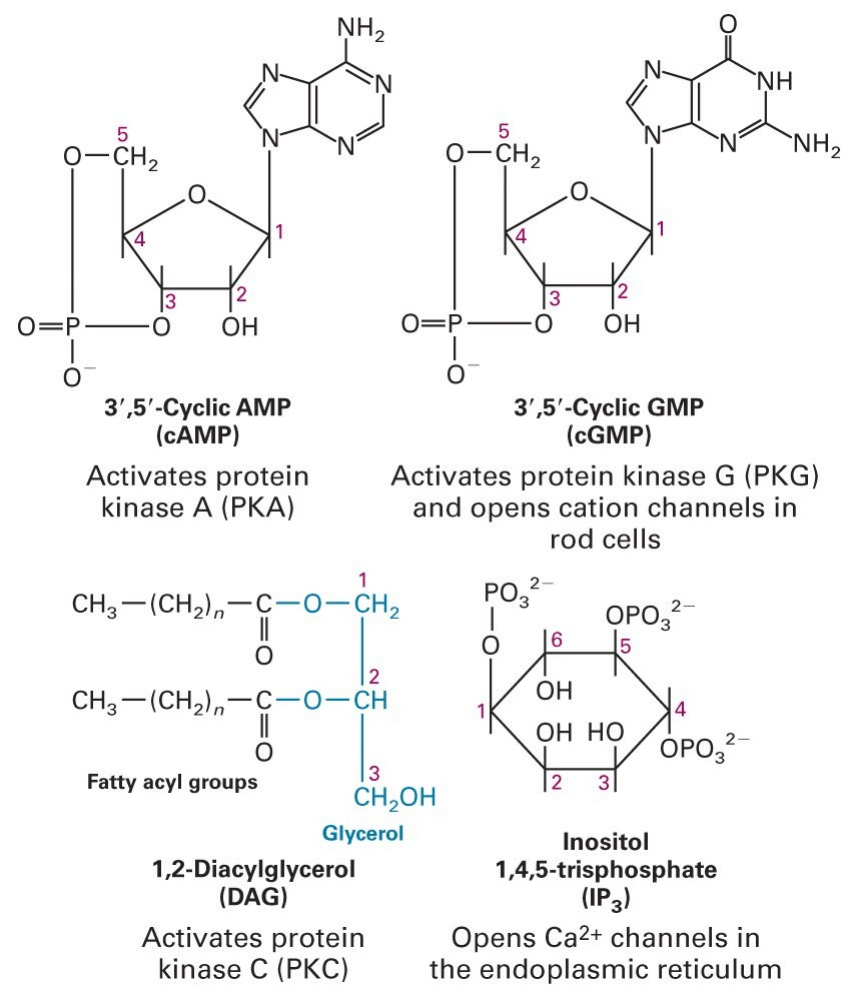
- Because of so many stages in the process, there are many possibilities
  - The same signaling molecule can target different receptor molecules – might have different affinity sites or the same site might be active
  - Some receptors can initiate action via more than one intracellular signaling pathway
    - Modulate ion-channels
    - Modulate activity of proteins
    - Modulate activity of protein synthesis (!)
    - Trigger protein expression

Some messenger molecules

- Epinephrine
  - Heart – increase in rate and contraction strength
  - Smooth muscles – decrease in tension
  - Liver – increase in conversion of glycogen to glucose
- Acetycholine
  - Muscle – contraction
  - Heart – decreases rate and force
  - Pancreas – induces insulin secretion

Why different effects? Look at receptors & signaling cascades

Some effector molecules



Receptor classes & signaling pathways -1

TABLE 14-1 Overview of Major Receptor Classes and Signaling Pathways

Receptor Class/Pathway*	Distinguishing Characteristics
RECEPTORS LINKED TO TRIMERIC G PROTEINS	
G protein–coupled receptors (13)	*Ligands:* Epinephrine, glucagon, serotonin, vasopressin, ACTH, adenosine, and many others (mammals); odorant molecules, light; mating factors (yeast) *Receptors:* Seven transmembrane α helices; cytosolic domain associated with a membrane-tethered trimeric G protein *Signal transduction:* (1) Second-messenger pathways involving cAMP or IP_3/DAG; (2) linked ion channels; (3) MAP kinase pathway

Receptor classes & signaling pathways -2

TABLE 14-1 Overview of Major Receptor Classes and Signaling Pathways

Receptor Class/Pathway*	Distinguishing Characteristics
RECEPTORS WITH INTRINSIC OR ASSOCIATED ENZYMATIC ACTIVITY	
TGFβ receptors (14, 15)	*Ligands:* Transforming growth factor β superfamily (TGFβ, BMPs), activin, inhibins (mammals); Dpp (*Drosophila*) *Receptors:* Intrinsic protein serine/threonine kinase activity in cytosolic domain (type I and II) *Signal transduction:* Direct activation of cytosolic Smad transcription factors
Cytokine receptors (14, 15)	*Ligands:* Interferons, erythropoietin, growth hormone, some interleukins (IL-2, IL-4), other cytokines *Receptors:* Single transmembrane α helix; conserved multi-β strand fold in extracellular domain; JAK kinase associated with intracellular domain *Signal transduction:* (1) Direct activation of cytosolic STAT transcription factors; (2) PI-3 kinase pathway; (3) IP_3/DAG pathway; (4) Ras-MAP kinase pathway
Receptor tyrosine kinases (14)	*Ligands:* Insulin, epidermal growth factor (EGF), fibroblast growth factor (FGF), neurotrophins, other growth factors *Receptor:* Single transmembrane α helix; intrinsic protein tyrosine kinase activity in cytosolic domain *Signal transduction:* (1) Ras–MAP kinase pathway; (2) IP_3/DAG pathway; (3) PI-3 kinase pathway
Receptor guanylyl cyclases (13)	*Ligands:* Atrial natriuretic factor and related peptide hormones *Receptor:* Single transmembrane α helix; intrinsic guanylate cyclase activity in cytosolic domain *Signal transduction:* Generation of cGMP
Receptor phosphotyrosine phosphatases	*Ligands:* Pleiotrophins, other protein hormones *Receptors:* Intrinsic phosphotyrosine phosphatase activity in cytosolic domain inhibited by ligand binding *Signal transduction:* Hydrolysis of activating phosphotyrosine residue on cytosolic protein tyrosine kinases
T-cell receptors	*Ligands:* Small peptides associated with major histocompatability (MHC) proteins in the plasma membrane of macrophages and other antigen-presenting cells *Receptors:* Single transmembrane α helix; several protein kinases associated with cytosolic domain; found only on T lymphocytes *Signal transduction:* (1) Activation of cytosolic protein tyrosine kinases; (2) PI-3 kinase pathway; (3) IP_3/DAG pathway; (4) Ras–MAP kinase pathway

Receptor classes & signaling pathways -3

TABLE 14-1 Overview of Major Receptor Classes and Signaling Pathways

Receptor Class/Pathway*	Distinguishing Characteristics
RECEPTORS THAT ARE ION CHANNELS	
Ligand-gated ion channels (7, 13)	*Ligands:* Neurotransmitters (e.g., acetylcholine, glutamate), cGMP, physical stimuli (e.g., touch, stretching), IP_3 (receptor in ER membrane) *Receptors:* Four or five subunits with a homologous segment in each subunit lining the ion channel *Signal transduction:* (1) Localized change in membrane potential due to ion influx, (2) elevation of cytosolic Ca^{2+}

Receptor classes & signaling pathways -4

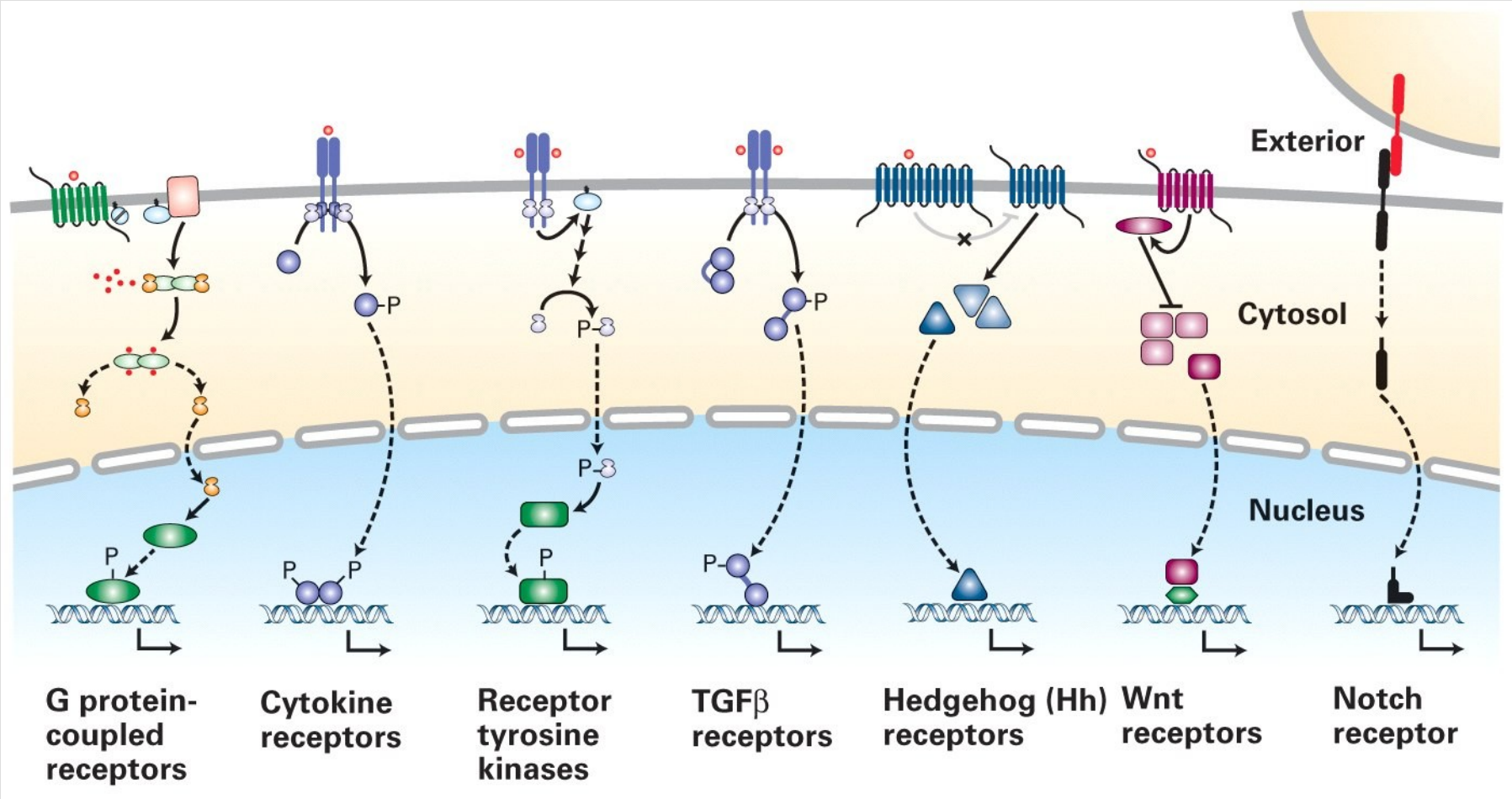
TABLE 14-1 Overview of Major Receptor Classes and Signaling Pathways

Receptor Class/Pathway*	Distinguishing Characteristics
INTRACELLULAR RECEPTORS PATHWAYS	
Nitric oxide pathway (13)	*Ligands:* Nitric oxide (NO) *Receptor:* Cytosolic guanylyl cyclase *Signal transduction:* Generation of cGMP
Nuclear receptor pathways (11)	*Ligands:* Lipophilic molecules including steroid hormones, thyroxine, retinoids, and fatty acids in mammals and ecdysone in *Drosophila* *Receptors:* Highly conserved DNA-binding domain, somewhat conserved hormone-binding domain, and a variable domain; located within nucleus or cytosol *Signal transduction:* Activation of receptor's transcription factor activity by ligand binding

*Unless indicated otherwise, receptors are located in the plasma membrane. Numbers in parentheses indicate chapters in which a receptor/pathway is discussed in depth.

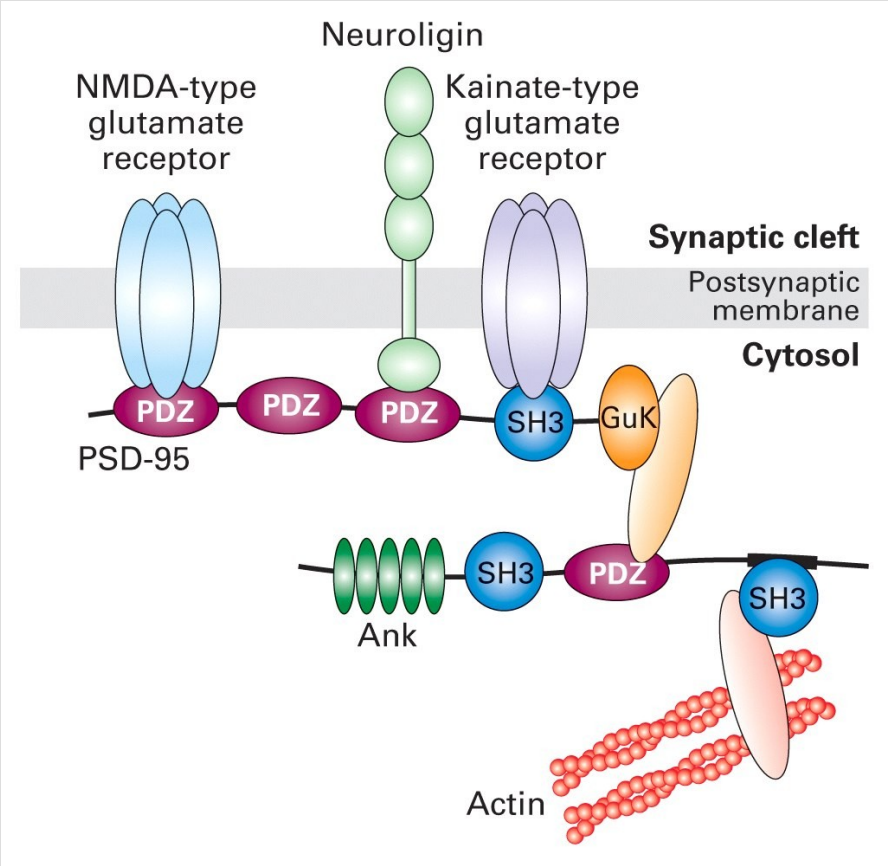
SOURCES: J. Gerhart, 1999, *Teratology* **60**:226, and A. Brivanlou and J. E. Darnell, 2002, *Science* **295**:813.

Possibilities

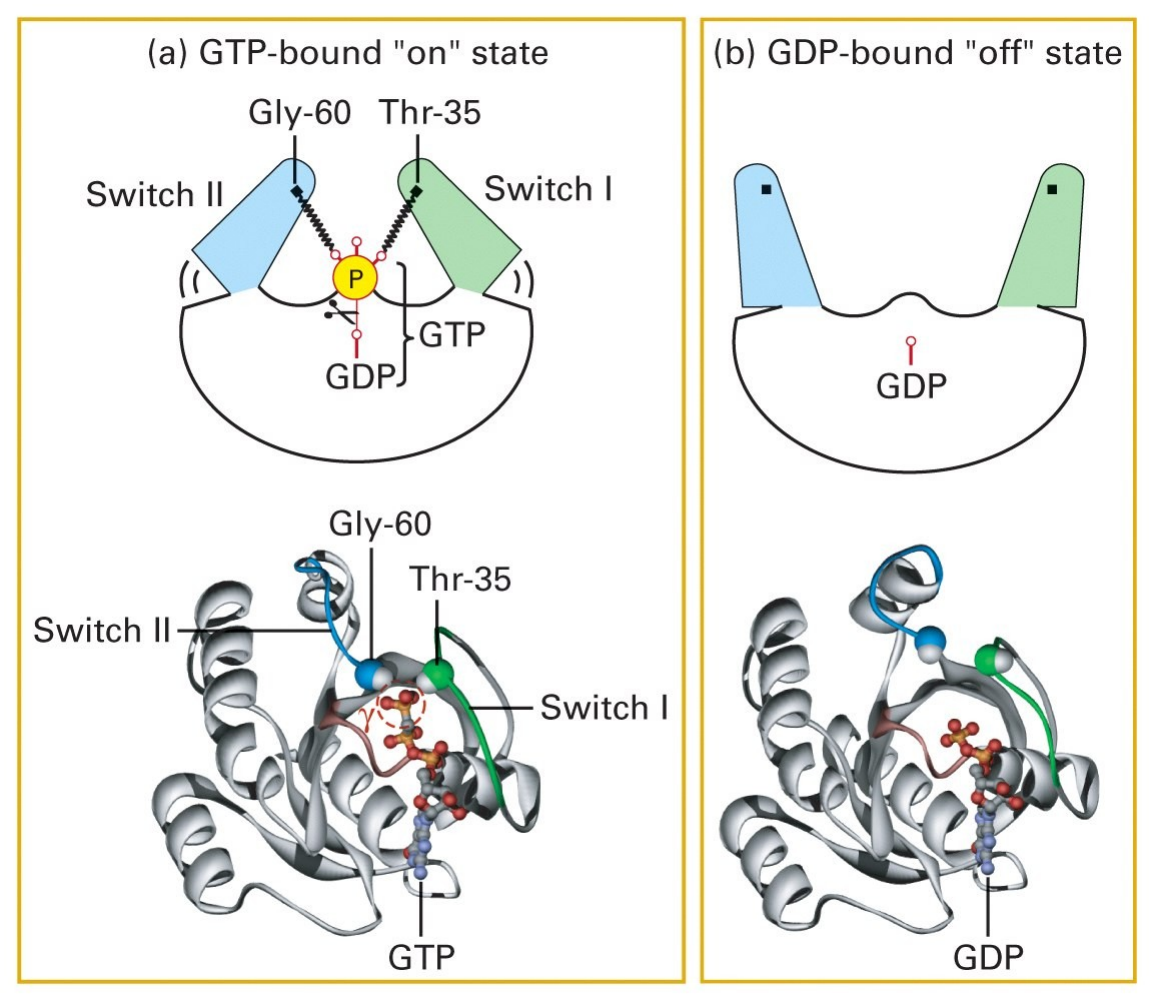


Organization of receptors

- Receptors often areally localized and areally organized
- Sometimes both areally and spatially organized



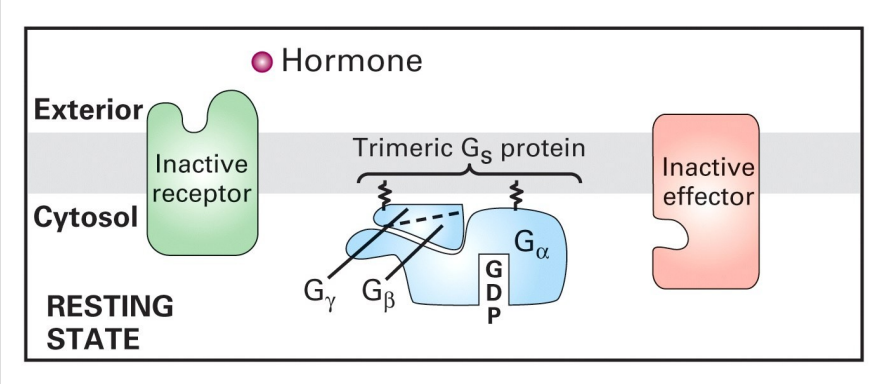
An example of how switching occurs

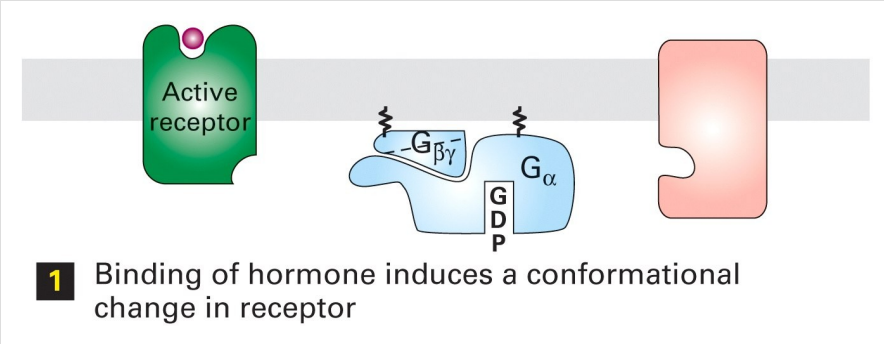


G-protein

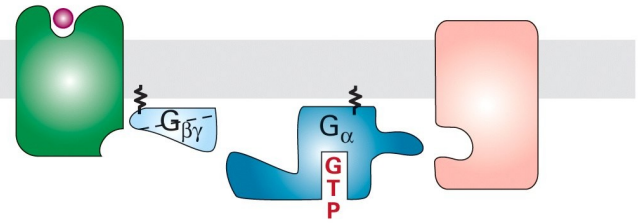
- Uses the GDP to GTP switch of state to activate an enzyme that catalyzes cyclic AMP for further signaling

G-protein action -1

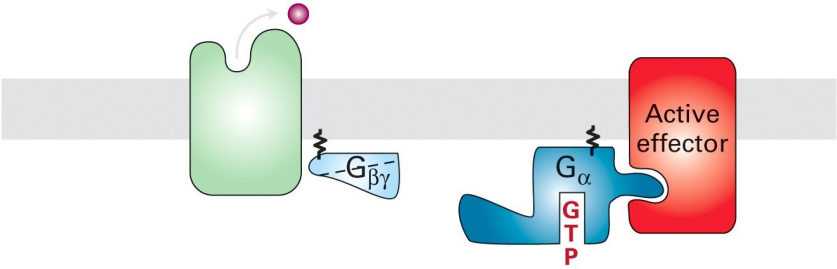




G-protein action -2



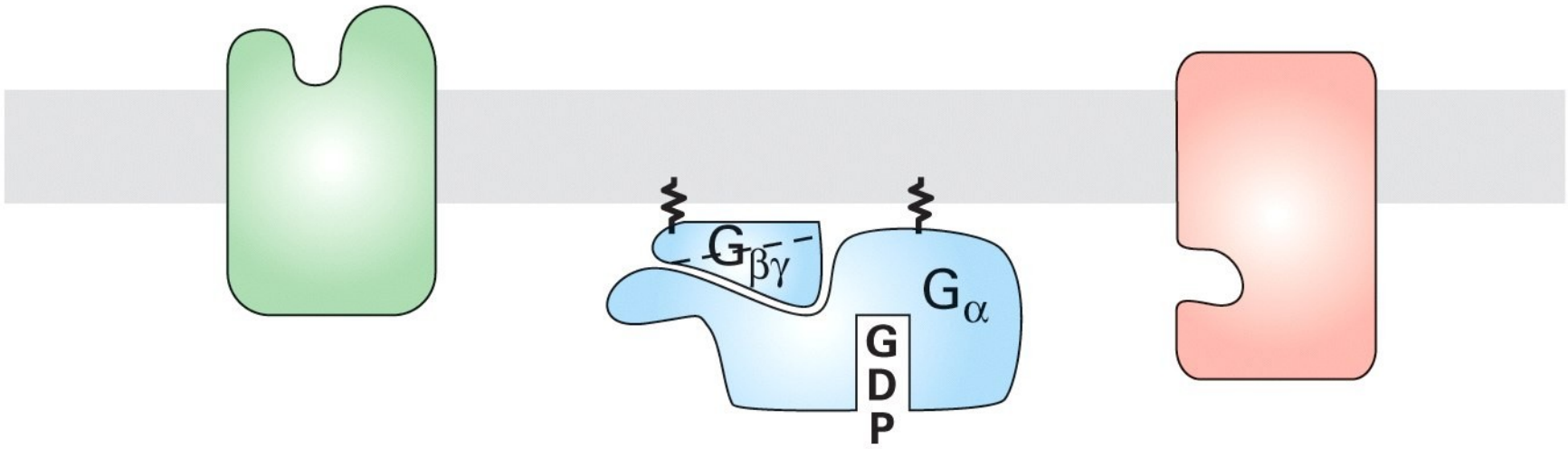
3 Binding induces conformational change in G_α; bound GDP dissociates and is replaced by GTP; G_α dissociates from $G_{\beta\gamma}$



4 Hormone dissociates from receptor; G_α binds to effector, activating it

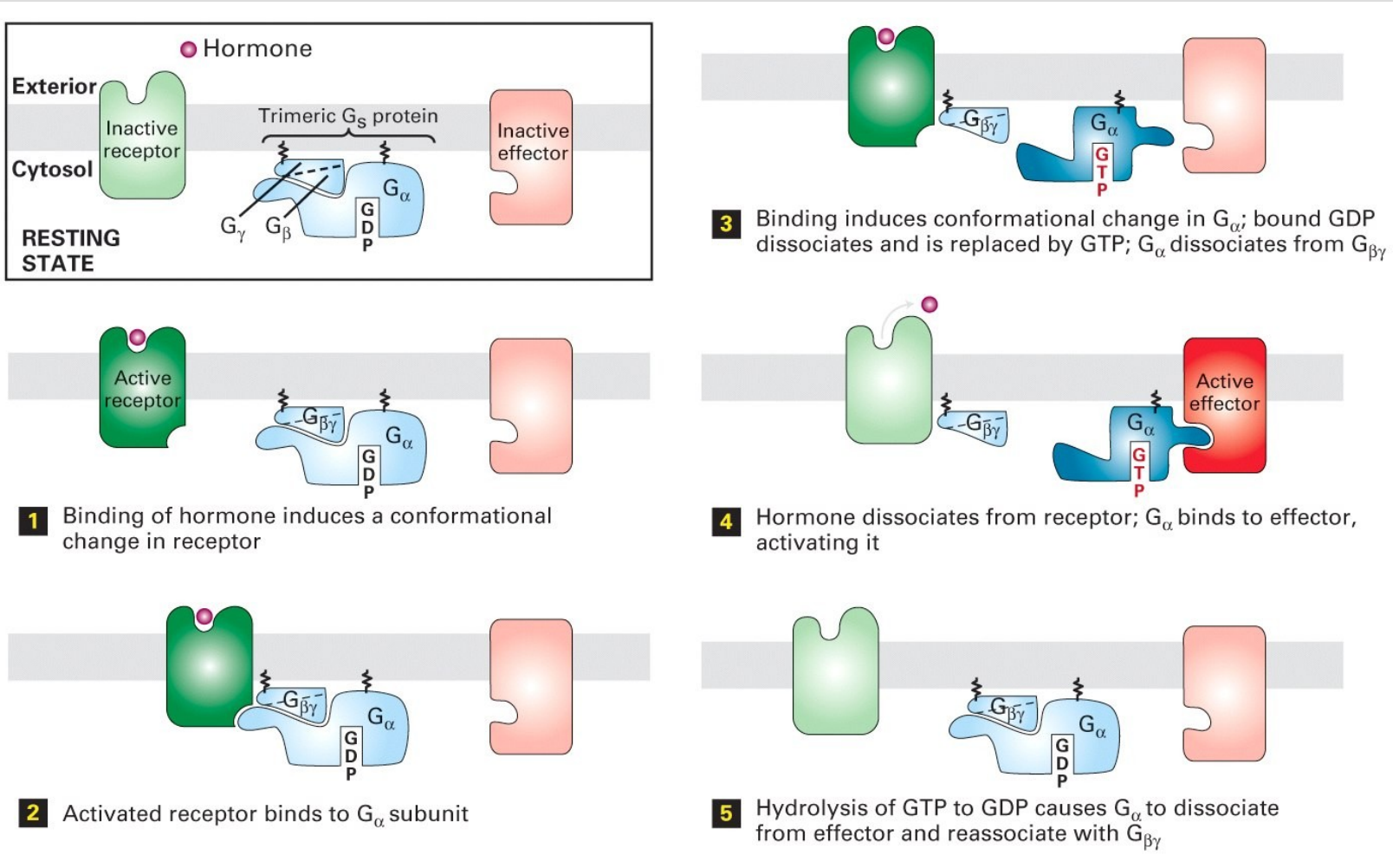
Is the ligand affinity constant state dependent?

G-protein action -3

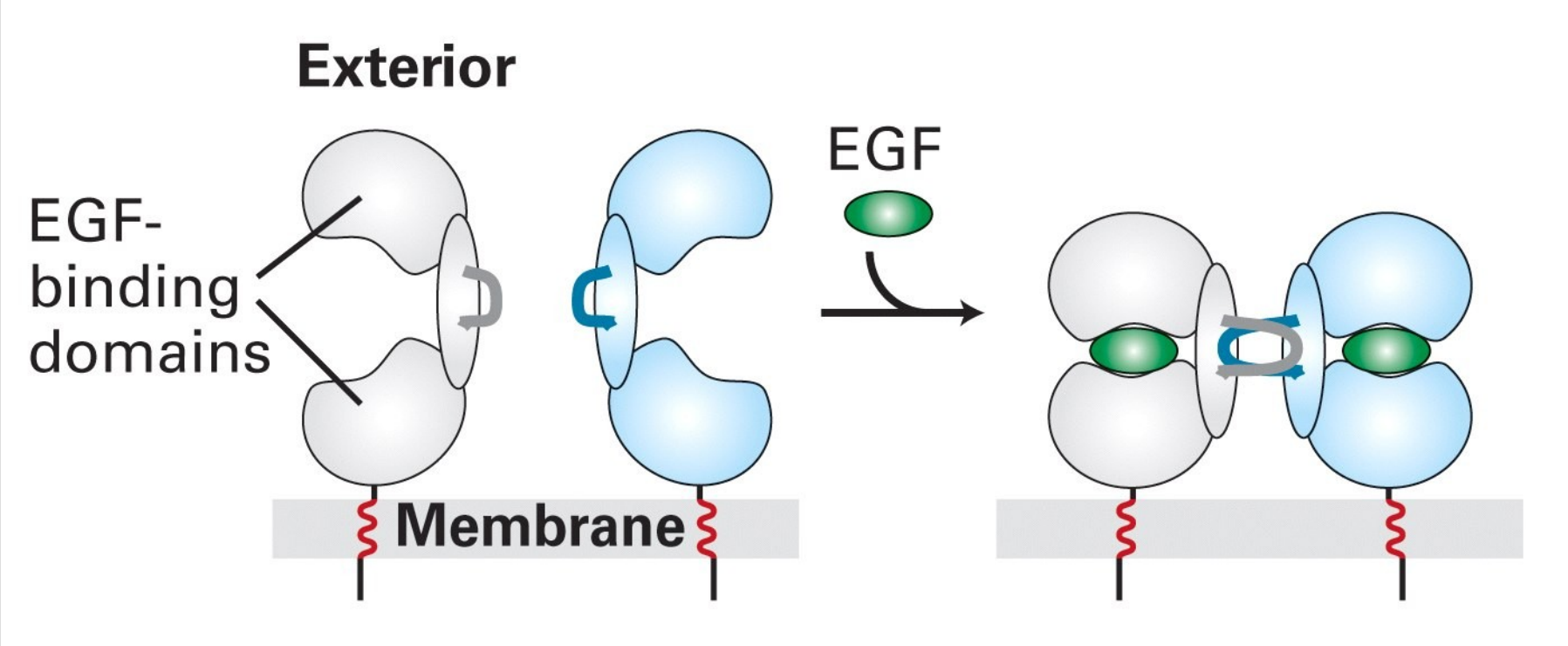


5 Hydrolysis of GTP to GDP causes G_α to dissociate from effector and reassociate with $G_{\beta\gamma}$

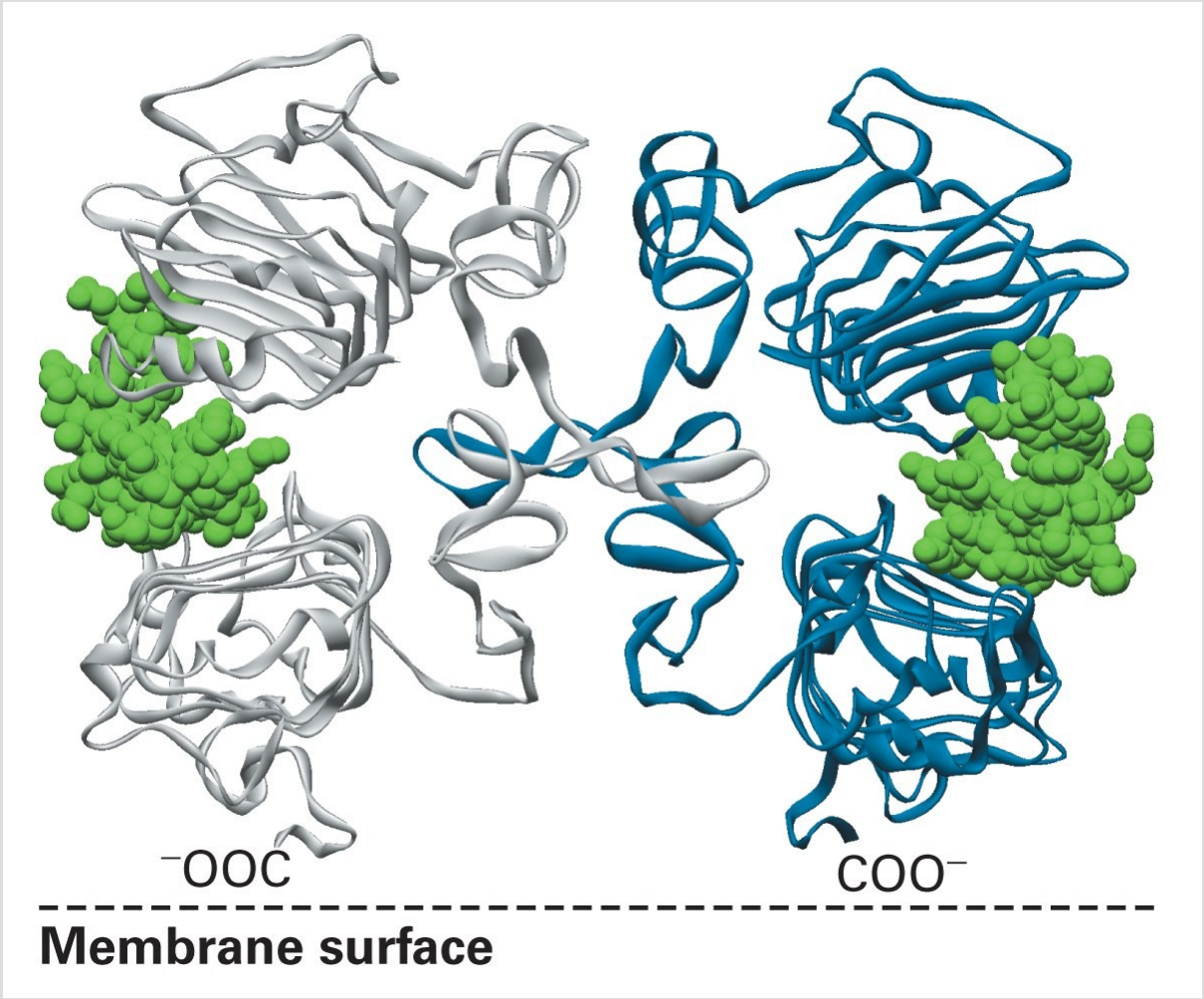
G-protein action



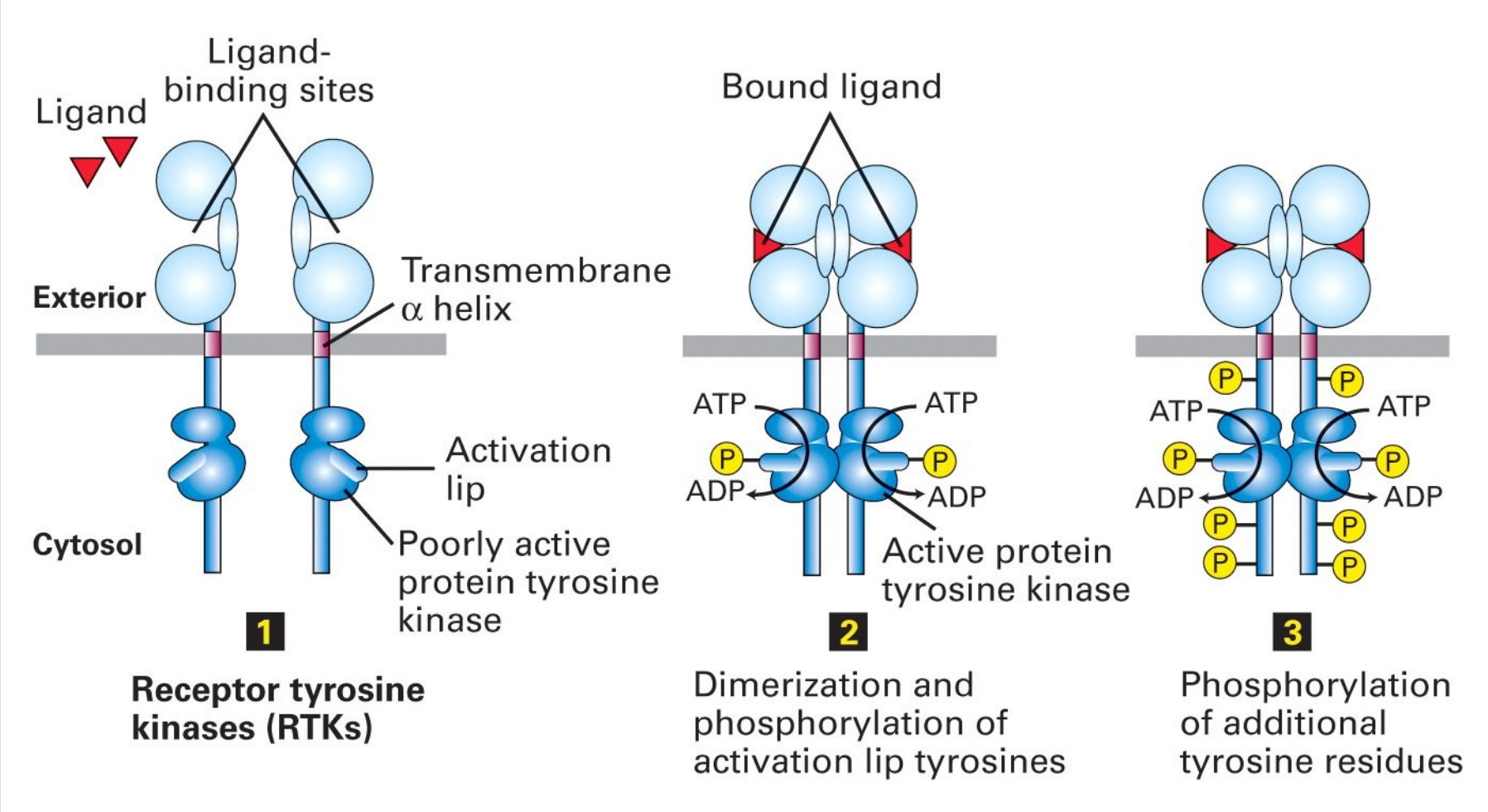
Other effector processes



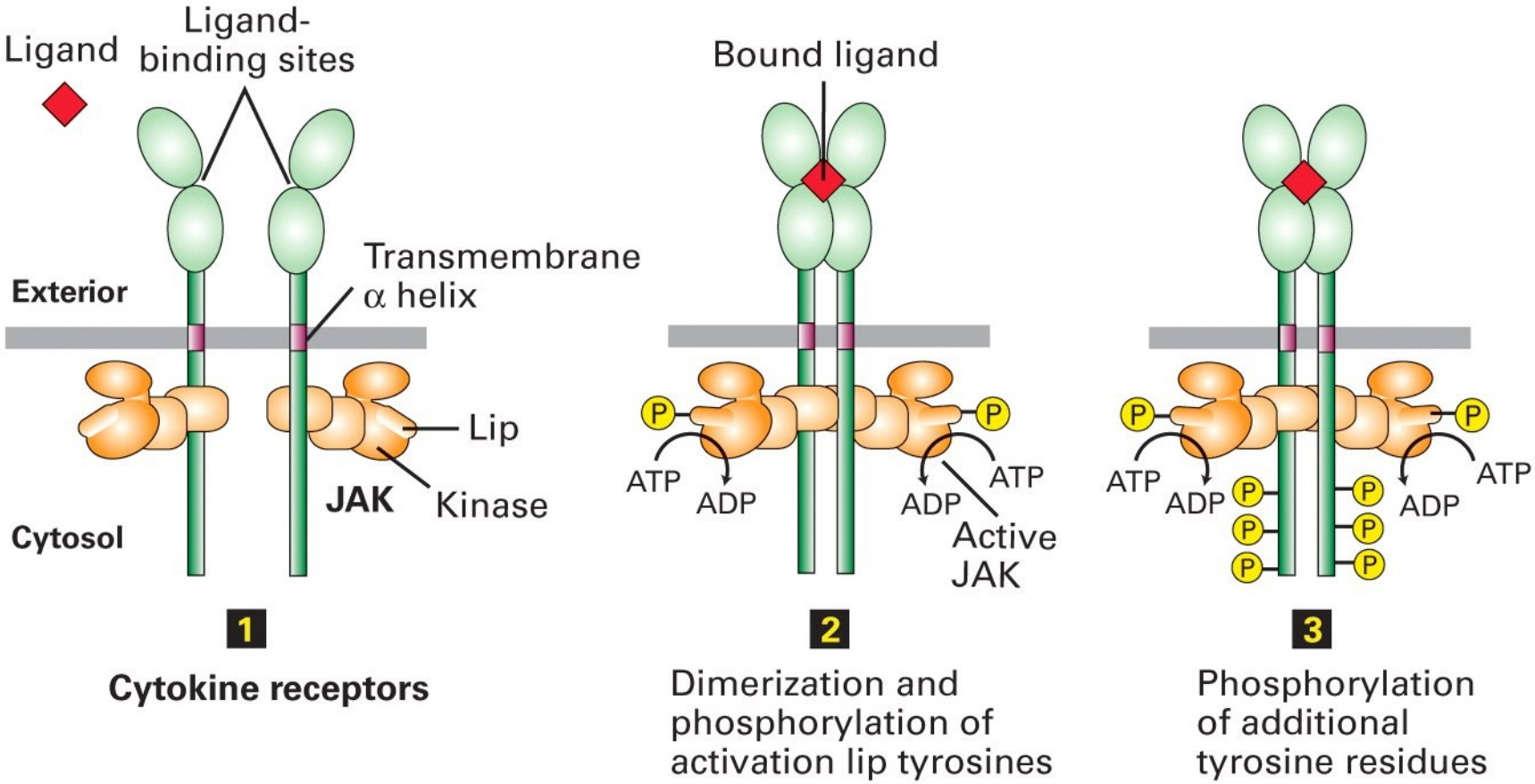
Cartoon & molecular structure correspondence



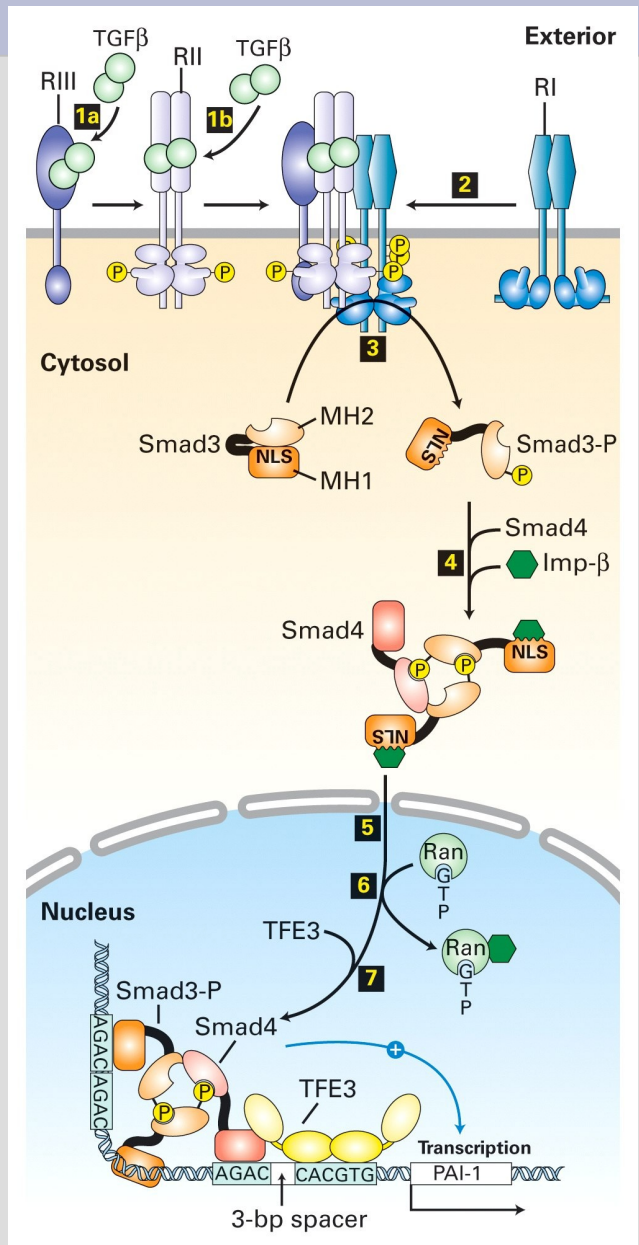
Phosphorylation based processes -1



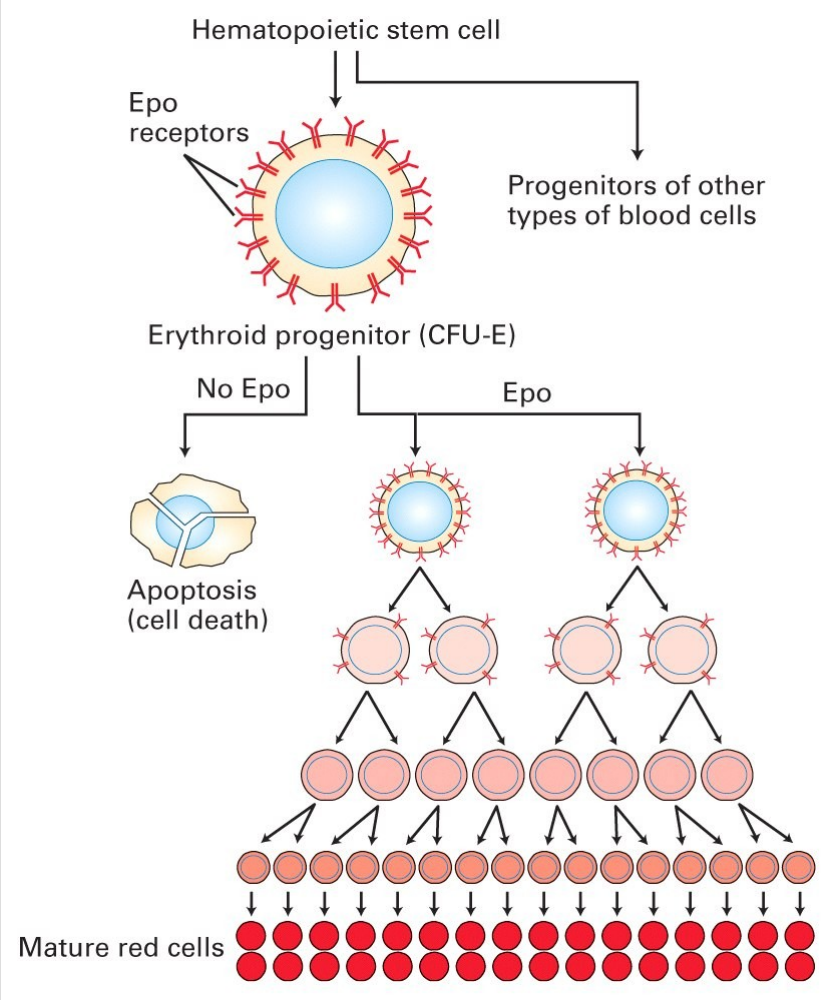
Phosphorylation based processes -2



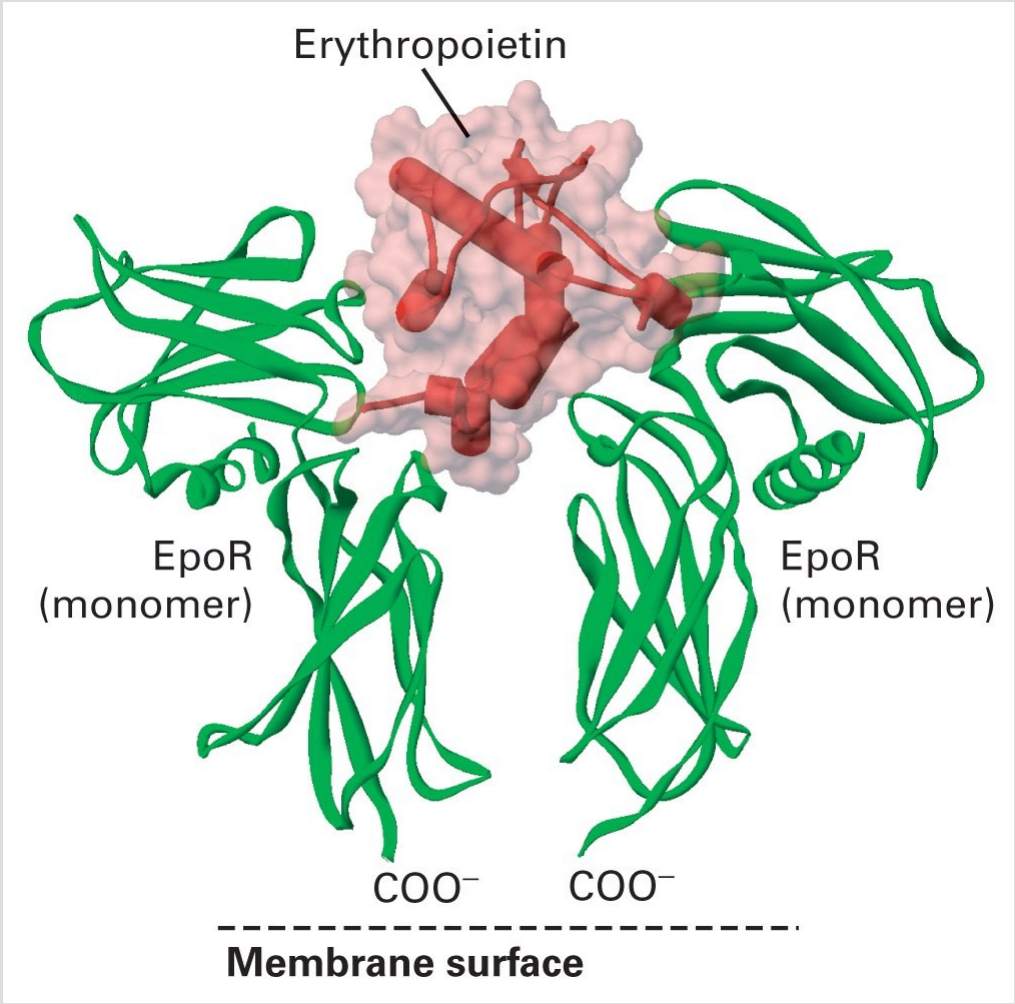
Control of gene expression



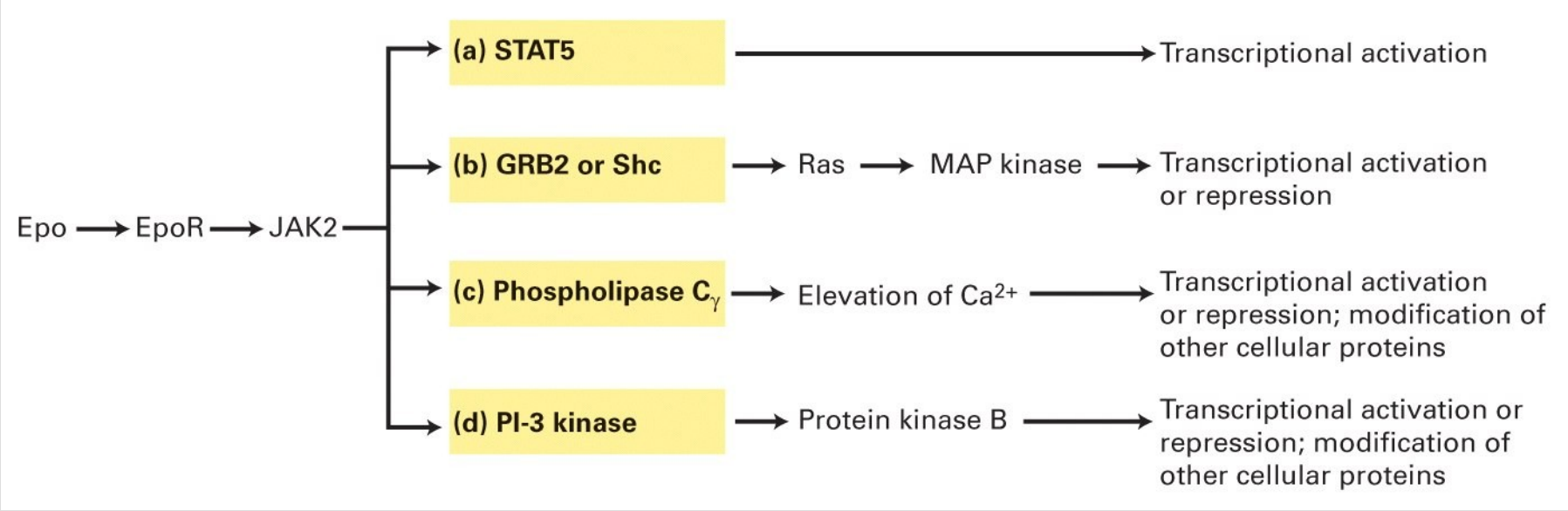
Erythropoeitin & red cell production



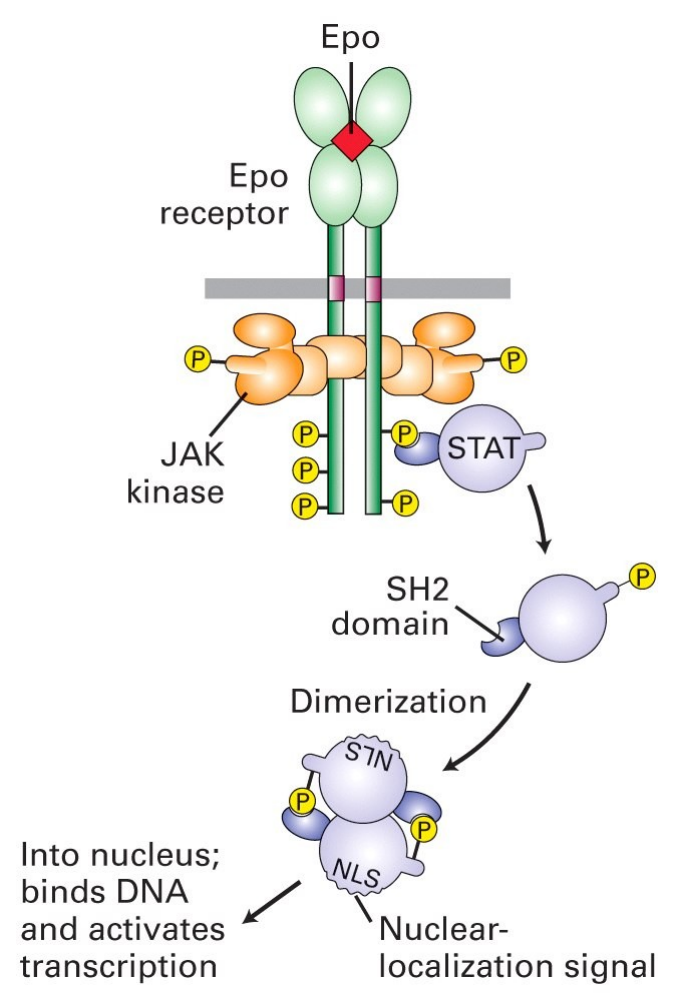
Erythropoitin structure



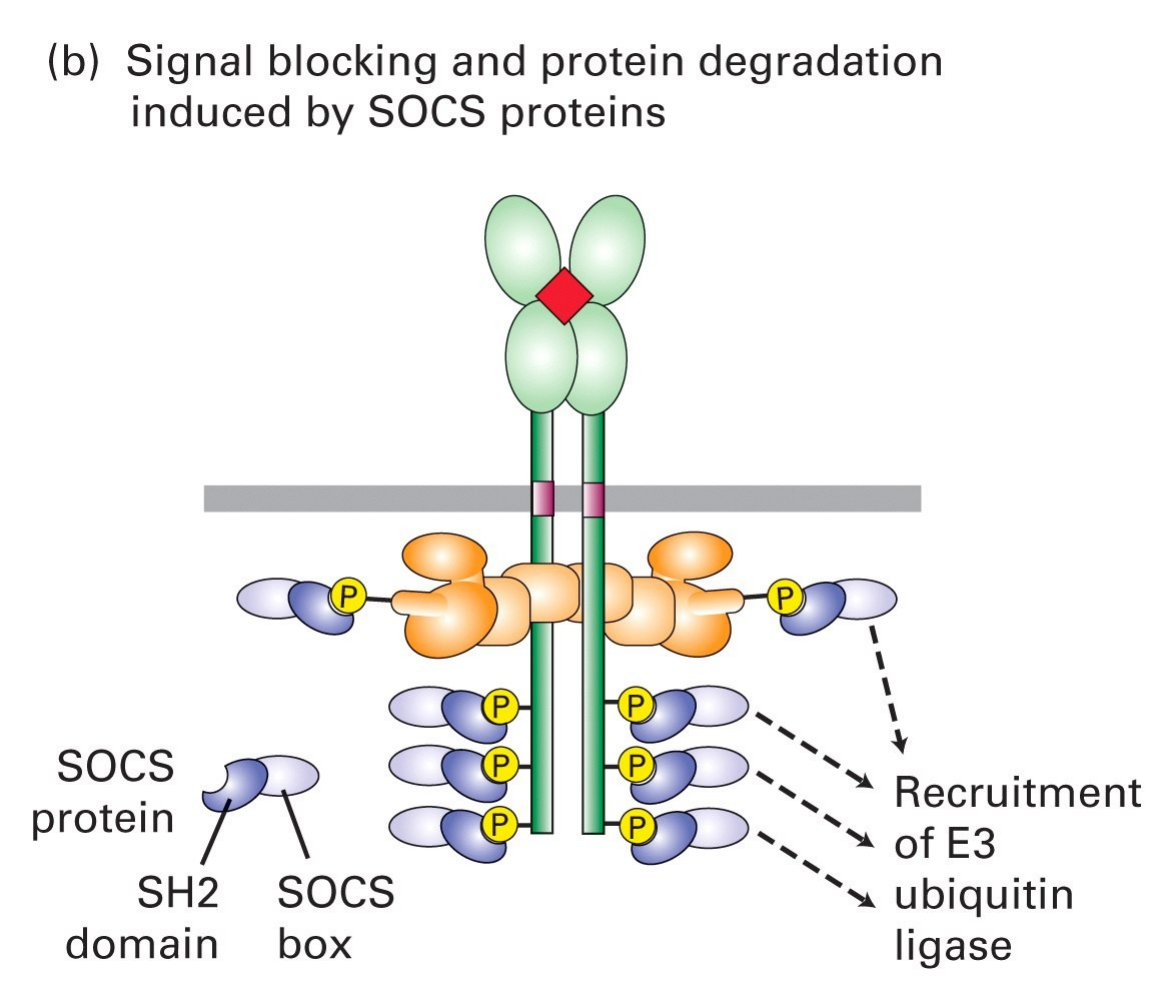
Different signaling cascades initiated by Epo



Triggering transcription

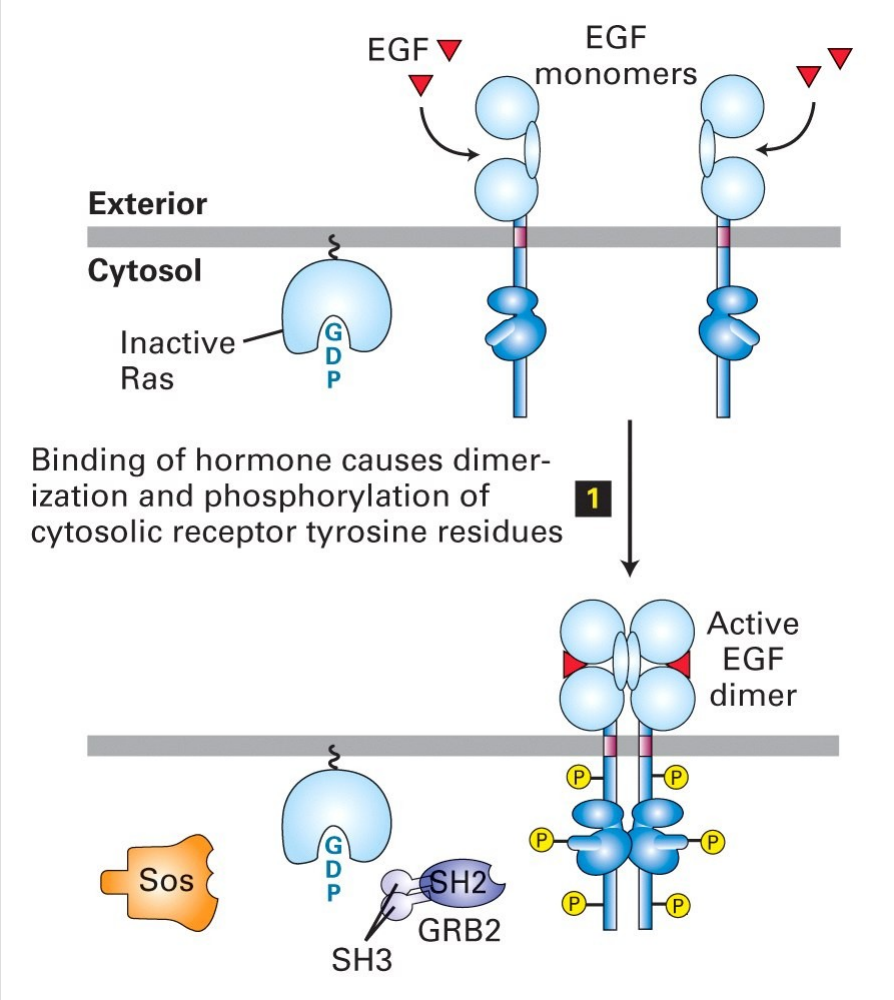


Signal blocking & protein degradation



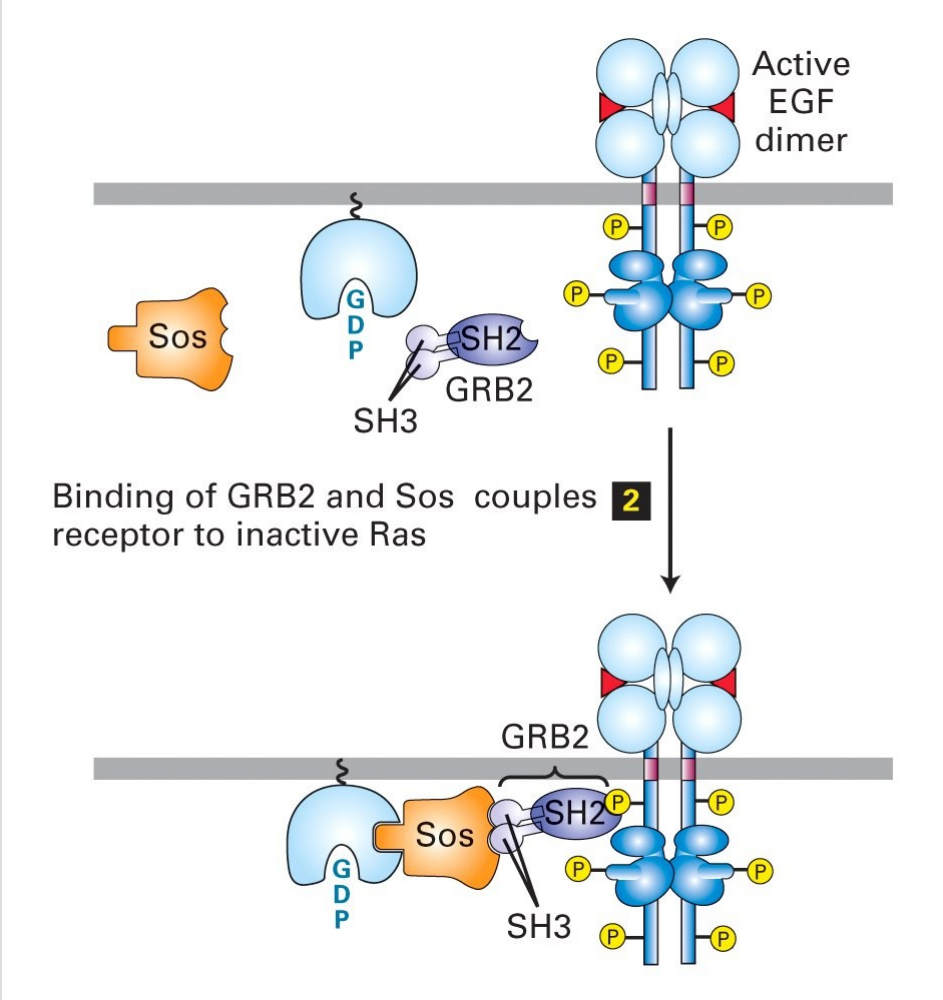
Poly-ubiquitin based tagging & degradation of proteins

Ras pathway -1

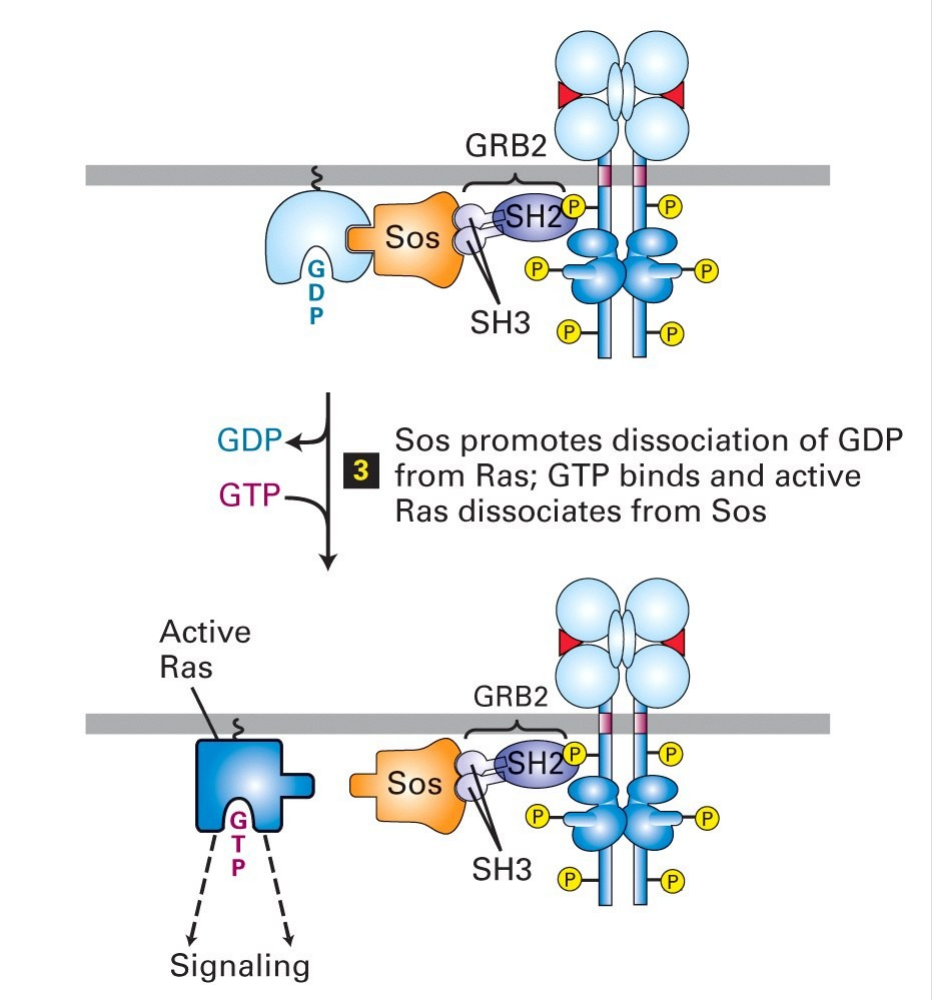


Why does phosphorylation happen?

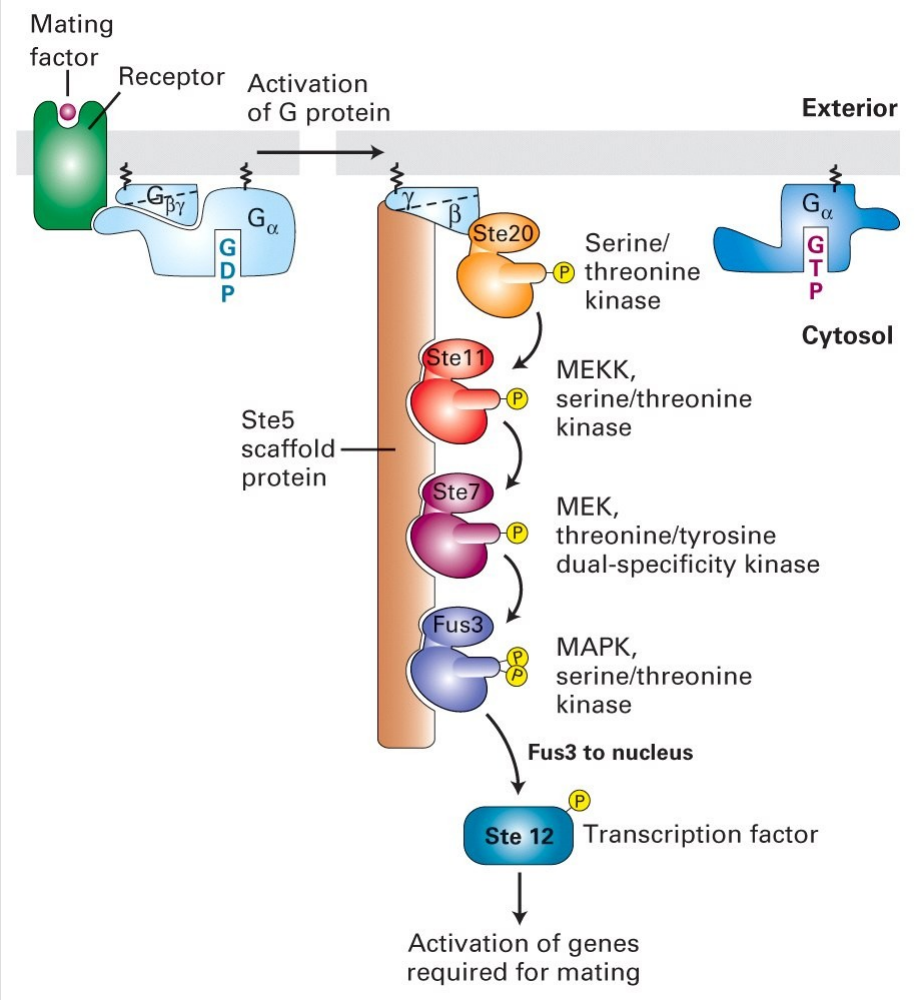
Ras pathway -2



Ras pathway -3

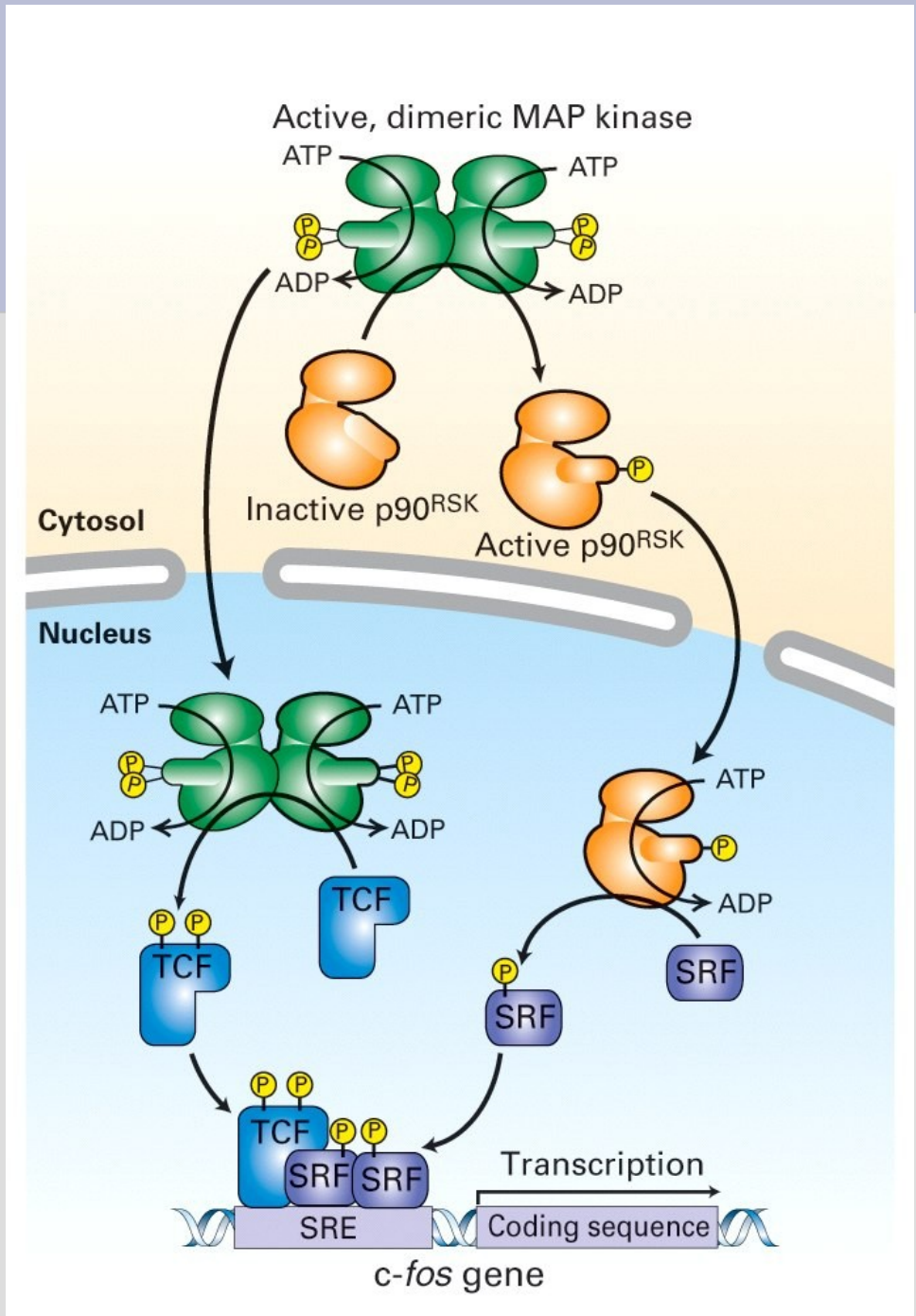


More complex cascade



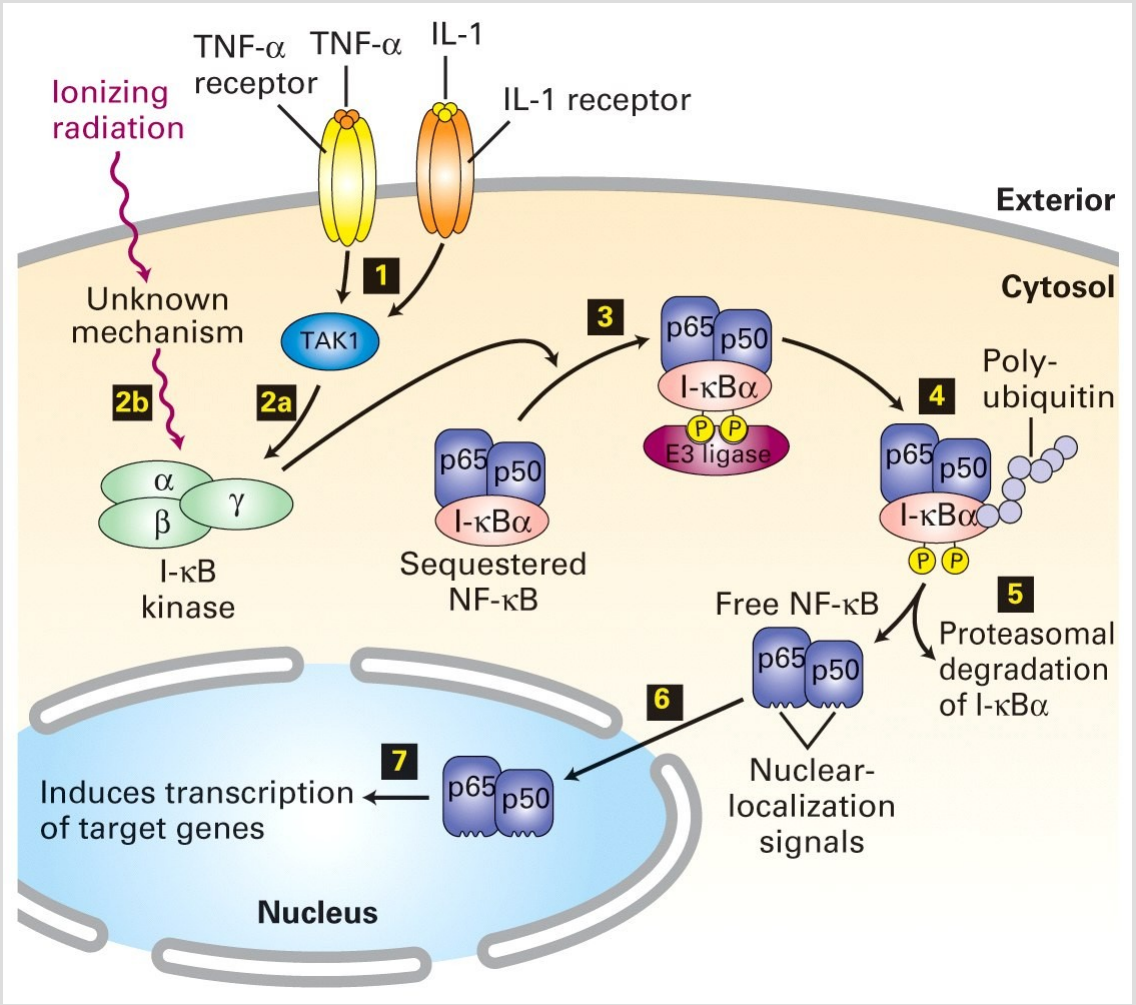
Effecting control

Should we look at mathematically modeling this?

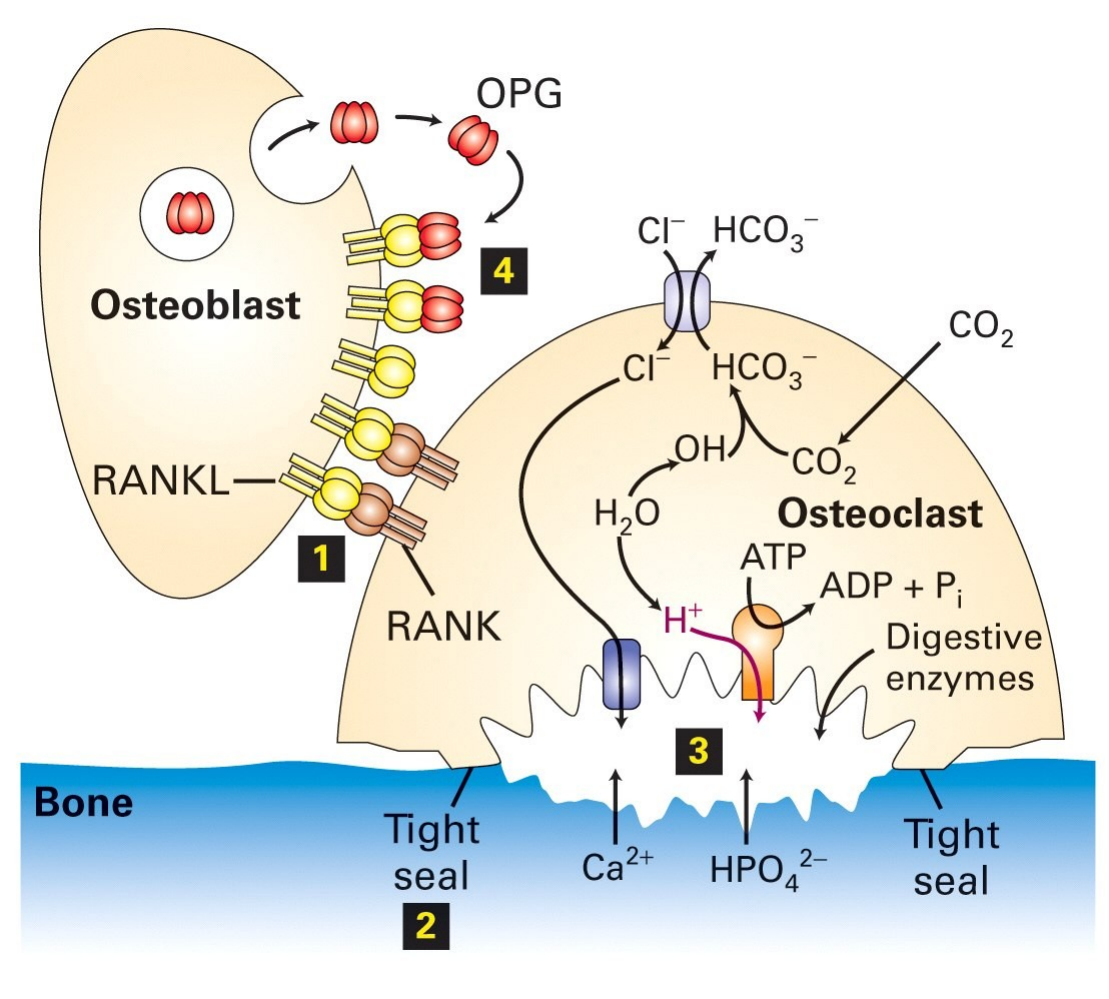


TAK1 & cell survival signaling

[Transforming growth factor β -activated kinase]

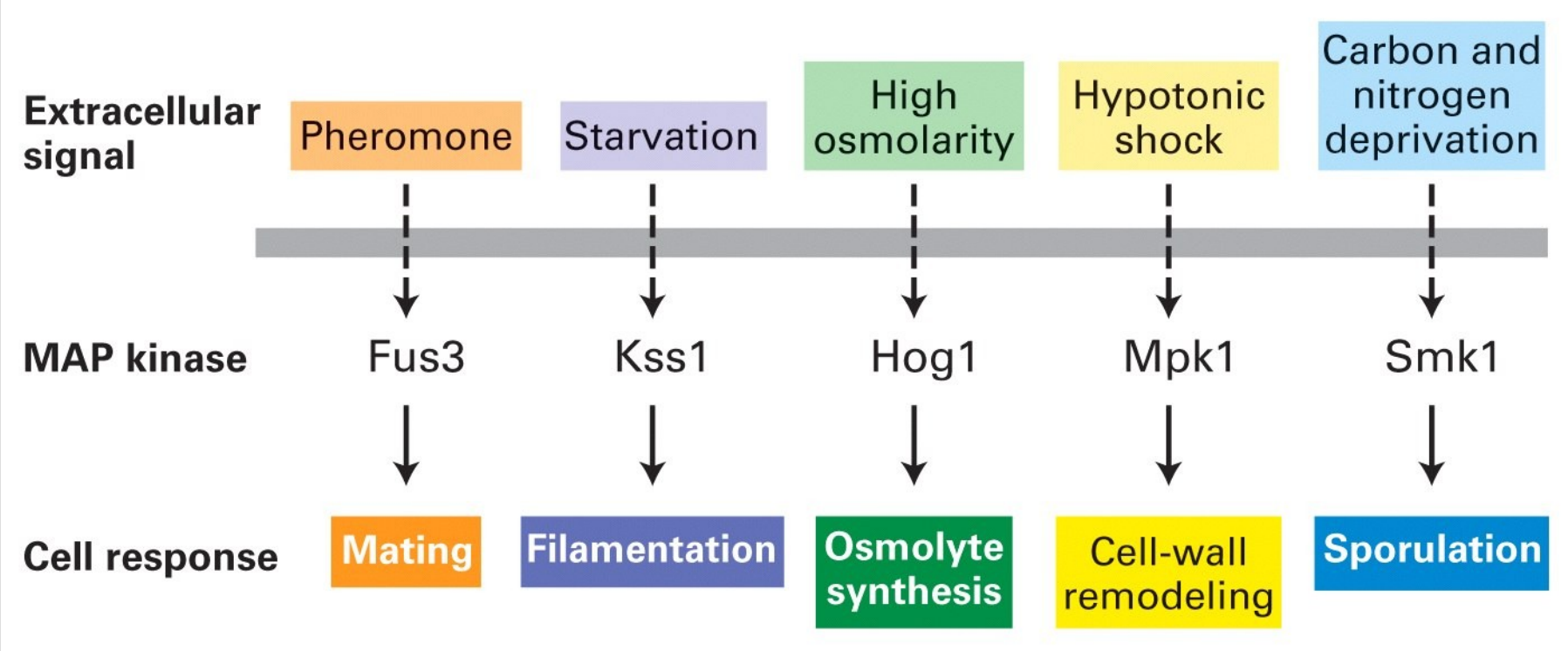


Bone shaping – resorption here

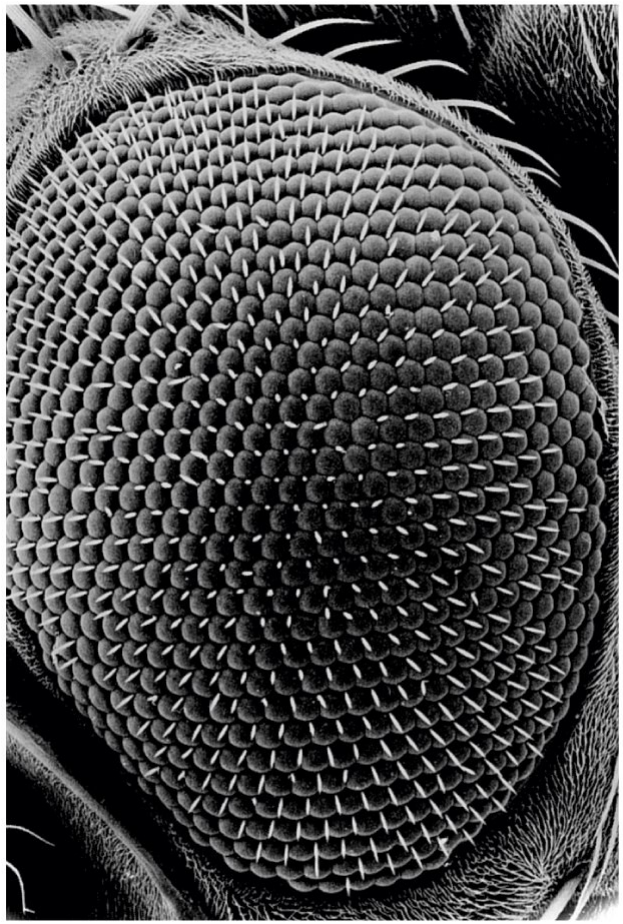


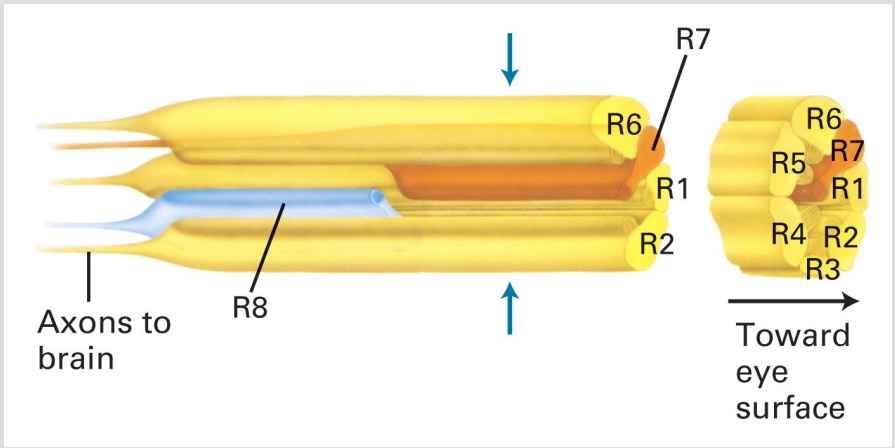
What happens to the Ca?

Responses of yeast to different stimuli



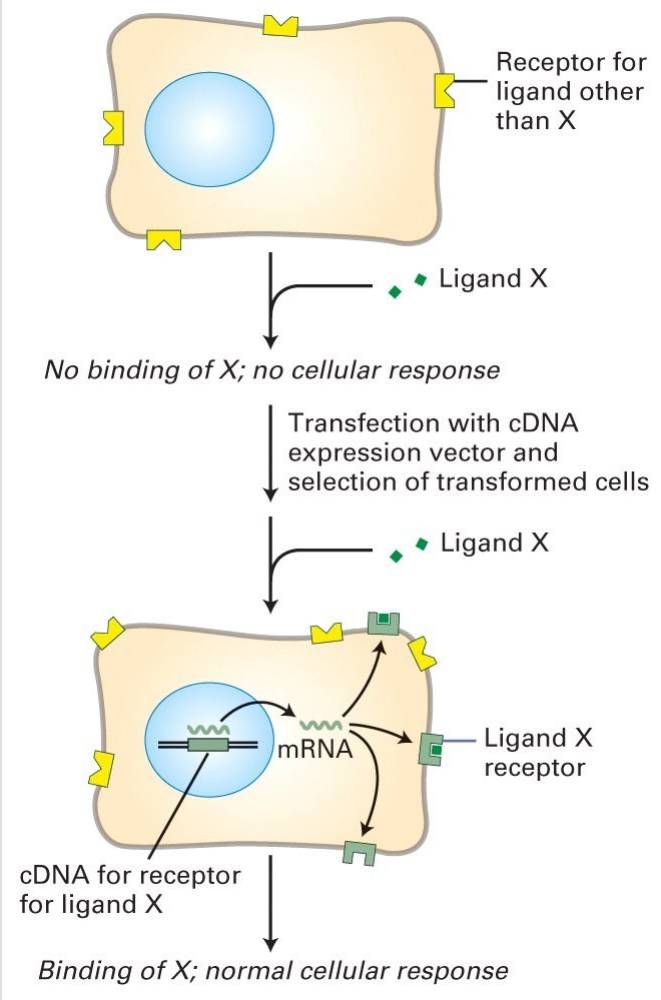
Studies complex: Example rods





Expression of G protein-regulated phospholipase C (PLC) β4 controls activity of retinal signaling but not initial change of potential

How studied


Receptor for ligand other than X
Ligand X
No binding of X; no cellular response
Transfection with cDNA expression vector and selection of transformed cells
Ligand X
mRNA
Ligand X receptor
cDNA for receptor for ligand X
Binding of X; normal cellular response

Summary

- Chemical signaling a cascade of signals
  - First messenger binds to receptor --> Second messenger released or a conformation change leads to an effector modulating a regulatory molecule
- Few signaling motifs but enable many possibilities
- Could model a signaling cascade mathematically for fun